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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,399	02/11/2005	Andreas Krause	TX/4-32608A	6111

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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	PAPER NUMBER
1636	

MAIL DATE	DELIVERY MODE
10/29/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,399	KRAUSE ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 8-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 8-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Examiner of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Jennifer Dunston, Art Unit 1636.

This action is in response to the amendment, filed 4/24/2008, in which claims 5-7 were canceled, and claims 1-4 and 8-11 were amended. Currently, claims 1-4 and 8-11 are pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

Priority

Claims 1-4 and 8-11 receive the benefit of U.S. Provisional Application No. 60/405,225, filed 8/22/2002.

Claim Rejections - 35 USC § 112

The rejection of claim 7 under 35 U.S.C. 112, second paragraph, is moot in view of Applicant's cancellation of the claim in the reply filed 4/24/2008. The rejection of claim 7 has been withdrawn.

The rejection of claims 5-7 under 35 U.S.C. 112, first paragraph (enablement), is moot in view of Applicant's cancellation of the claims in the reply filed 4/24/2008. The rejection of claims 5-7 has been withdrawn.

Claims 1-4 and 8-11 **stand rejected** under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's arguments filed 4/24/2008 have been fully considered but they are not persuasive.

A. *The Scope of the Claims*

The response notes that the claims have been amended to recite that the transplanted subject must be a kidney transplanted subject. Further, the response notes that the claims require the mRNAs, proteins, genes or gene products that are measured/compared and/or regulated to correspond to, be encoded by, or actually be the nucleic acid sequences set forth in Table 3. Thus, the response asserts that the scope of the claims in relation to the type of transplanted subject, and the mRNA, protein, gene or gene product has been significantly narrowed to overcome the rejection of record. While claims 1-4 and 8-11 have been amended to require the control sample and test sample to be a renal allograft tissue biopsy, claim 3 is still readable upon the use of any tissue sample. The claims encompass the use of a sample from any species of organism. While the sequences of SEQ ID NOs: 29-38 are human mRNA sequences, the claims encompass sequences "corresponding to" SEQ ID NOs: 29-38. The specification does not provide an explicit definition for "corresponding to." Given the broadest reasonable

interpretation of the term, the correspondence does not have to be direct. In other words, the claims encompass the use of sequences that correspond to SEQ ID NOs: 29, 30, 31, 32, 33, 34, 35, 36, 37 and 38, where the sequences are homologs or other corresponding members of a gene family. Furthermore, the claims encompass the detection of SEQ ID NOs: 35 and 36 by reverse transcription PCR or quantitative PCR; however, the specification teaches that insufficient sequence data prevented the use these methods for AL049449 and W26469 (e.g., page 21).

The response notes that claims 3 and 4 are limited to a compound that is a "CR-inhibiting agent." The response explains that the CR-inhibiting agents are described by membership in two narrow functional classes: 1) they must be capable of modulating the synthesis, expression or activity of the nucleic acid sequences in Table 3; and 2) they must be a CR-inhibiting agent. Thus, the response asserts that the breadth of the claims is not unreasonable. This is not found persuasive, because the claims encompass the use of compounds defined primarily by function. The claims encompass the use of small molecules, antibodies, or other drug structures. The claims encompass a genus of compounds defined only by their function where the relationship between the structural features of the members of the genus and the function has not been defined. In the absence of such a relationship in the as-filed application or which would have been recognized based on information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition. The fact that one could have assayed a compound of interest for the claimed function does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound would fall within the scope of what is claimed.

B. *The Disclosure*

The response asserts that the specification discloses a sufficient number of nucleic acid sequences useful for the early diagnosis of CR in a kidney transplanted subject, nucleic acid sequences that may be used for monitoring CR in a kidney transplanted subject, and nucleic acid sequences that, when modulated, result in prevention, inhibition or reduction of CR. The response specifically points to Tables 1-3 for support of such sequences. Further, the response asserts that the use of the sequences for early diagnosis is supported by the specification at page 18, which states the following:

> By applying above method the expression levels of about 12,000 transcripts in serial renal allograft protocol biopsies from 17 transplant patients have been monitored. Demographic and clinical characteristics of all patients in this study are listed in Table 5. One group of patients developed CR within 6 months after the timepoint the biopsy was taken, the other group did not. Using the set of genes as disclosed, preferably the set of 10 genes as indicated in Table 3, as identified by detailed statistical analysis of the biopsy RNA expression profiles, the occurrence/non occurrence of chronic rejection was predicted in 15 out of these 17 patients (> 88 %). Furthermore, the set of discriminator genes was also able to predict that a month 12 biopsy belonged to a patient that developed CR until month 18.

This portion of the specification does not contradict the unpredictability set forth by Damrauer. The specification teaches that RNA was collected at three time points: at the time of transplantation (baseline), 6 months after transplantation, and 12 months after transplantation (e.g., page 9, 1st full paragraph). The specification does not teach which time points were used in the classification of the 17 transplant patients. The specification only envisions comparing the baseline of a control sample to a test sample (e.g., pages 3-4). The specification does not teach the comparison of a test sample taken at 6 months post-transplant to the expression data obtained from a population of control samples, where the control sample was obtained at 6 months post-transplant, and the control individuals do not develop chronic rejection. However, the post-filing

art teaches that this comparison at the 6 moth post-transplantation time point is what is required to use the claimed 10 genes as a predictor of chronic rejection (Scherer et al. Transplantation, Vol. 75, No. 8, pages 1323-1330, April 2003; e.g., page 1326, Results). Guidance with respect to selecting the 6 month post-transplantation time point for the control samples is lacking in the instant specification. Furthermore, the specification does not provide any evidence that the expression of the disclosed genes is predictably altered in response to effective treatment by a CR-inhibiting agent. The agents are not specifically disclosed, and their relationship to the disclosed genes has not been determined. Moreover, claim 3 has been amended to require the gene expression to be "a negative indication of CR in the kidney transplanted subject." The negative indication could be read as the absence of CR or could be read as an undesirable or negative outcome, which is the presence of CR. The outcome of the method is unpredictable. With respect to claim 4, the specification does not teach CR-inhibiting compounds that meet the functional limitations of the claims. There are no working examples where a compound has been used to prevent CR, to inhibit CR, to reduce CR, or to treat CR. As discussed above, it would require undue experimentation to identify those structures capable of performing the claimed function.

With respect to the claimed CR-inhibiting agents, the response asserts that the specification may omit what is well-known in the art. The response asserts that the use of immunosuppressants, renin inhibitors, and ACE inhibitors for treating chronic rejection is well-known in the art. There is no evidence on the record that these compounds alter the expression of SEQ ID NOs: 29-38 in a predictable manner. The response asserts that one could screen these compounds for the ability to alter gene expression. Given the unpredictable effect of any one

compound on gene expression in a particular cell type and the absence of any known structure with the claimed function, it would require undue burden to randomly screen compounds with known CR-inhibiting activity for the ability to predictably modulate the expression of SEQ ID NOs: 29-38 as required by the claims.

The response asserts that the design of CR-inhibitors such as antisense or siRNA molecules was within the skill of the art. It is noted that the response cites a post-filing article to support this assertion (Reynolds et al.). However, publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. *In re Gunn*, 537 F.2d 1123, 1128, 190 USPQ 402,405-06 (CCPA 1976); *In re Budnick*, 537 F.2d 535, 538, 190 USPQ 422, 424 (CCPA 1976). Even if the prior art was enabling for the rational design of siRNA molecules for SEQ ID NOs: 29-38, there is no evidence on the record that reduced expression of SEQ ID NOs: 29-38 results in the prevention, inhibition, reduction, and treatment of CR.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

The rejection of claims 5-7 under 35 U.S.C. 112, first paragraph (enablement), is moot in view of Applicant's cancellation of the claims in the reply filed 4/24/2008. The rejection of claims 5-7 has been withdrawn.

Claims 1-4 and 8-11 **stand rejected** under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's arguments filed 4/24/2008 have been fully considered but they are not persuasive.

Applicant's arguments directed to the description of nucleic acid sequences has been not been found persuasive in light of the claim amendments to encompass the use of sequences "corresponding to" SEQ ID NOs: 29-38. SEQ ID NOs: 29-38 are sequences transcribed from human genes. The claims encompass sequences of other species or homologs that correspond to the recited sequences. Applicants were not in possession of a representative number of sequences for all of the sequences claimed. For example, there is no evidence on the record that sequences corresponding to SEQ ID NO: 36 were known in the art at the time the invention was made.

Applicant's arguments directed to the claimed genus of CR-inhibiting agents have not been found persuasive. The response explains that the CR-inhibiting agents are described by membership in two narrow functional classes: 1) they must be capable of modulating the synthesis, expression or activity of the nucleic acid sequences in Table 3; and 2) they must be a CR-inhibiting agent. Thus, the response asserts that the breadth of the claims is not reasonable. This is not found persuasive, because the claims encompass the use of compounds defined primarily by function. The claims encompass the use of small molecules, antibodies, or other drug structures. The claims encompass a genus of compounds defined only by their function where the relationship between the structural features of the members of the genus and the function has not been defined. In the absence of such a relationship in the as-filed application or

which would have been recognized based on information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition. The fact that one could have assayed a compound of interest for the claimed function does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound would fall within the scope of what is claimed. Possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features. *See University of Rochester*, 358 F.3d at 927, 69 USPQ2d at 1895. Without a correlation between structure and function, the claim does little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. *See Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 ("definition by function … does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is"). The description of broad categories of molecules such as small molecules, antibodies or other therapeutic agent does not provide a specific structure that performs the claimed function. Thus, these broad classes of molecules do not constitute species that fall within the claimed genus. A single species that falls within the claimed genus has not been described by the specification or prior art.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Claim Rejections - 35 USC § 102

The rejection of claims 1, 3-5 and 10-11 under 35 U.S.C. 102(b) as being anticipated by Russell et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 4/24/2008.

Claim Rejections - 35 USC § 103

The rejection of claim 2 under 35 U.S.C. 103(a) as being unpatentable over Russell et al in view of Damrauer et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 4/24/2008.

The rejection of claim 6 under 35 U.S.C. 103(a) as being unpatentable over Russell et al in view of Strehlau et al is moot in view of Applicant's cancellation of the claim in the reply filed 4/24/2008. The rejection of claim 6 has been withdrawn.

The rejection of claims 8-9 under 35 U.S.C. 103(a) as being unpatentable over Russell et al in view of Bennett et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 4/24/2008.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston, Ph.D.
Examiner
Art Unit 1636

/JD/

/Celine X Qian Ph.D./
Primary Examiner, Art Unit 1636